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FINAL

QUANTIFICATION OF TOXICOLOGICAL EFFECTS

FOR

DICHLOROMETHANE

Health and Ecological Criteria Division
Office of Science and Technology
Office of Water
U.S. Environmental Protection Agency
Washington, DC.

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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish Maximum Contaminant Level Goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document was comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to April 1987; however, more recent data have been added during the review process and in response to public comments.

When adequate health effects data exist, Health Advisory values for less-than-lifetime exposures (One-day, Ten-day, and Longer-term, approximately 10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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QUANTIFICATION OF TOXICOLOGICAL EFFECTS FOR DICHLOROMETHANE

The source documents for background information used to develop this report on the quantification of toxicological effects for dichloromethane are the health assessment document (HAD) for dichlormethane (U.S. EPA, 1985a) and a subsequent addendum to the HAD (U.S. EPA, 1985b). In addition, some references published since 1985 are discussed.

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic effects occur, while carcinogens are assumed to act without a threshold.

To summarize the results of the quantification of toxicological effects, a One-day Health Advisory of 10,000 ug/L for a 10-kg child was calculated, based on an acute oral study in rats reported by Kimura et al. (1971). No suitable data for the derivation of a Ten-day Health Advisory were found in the available literature. A Longer-term Health Advisory of 2,000 was developed for a 10-kg child, based on a 90-day drinking water study in rats (Kirschman et al., 1986). A Drinking Water Equivalent Level (DWEL) of 2,000 ug/L for a 70-kg adult was calculated based on a 2-year drinking water study in rats (Serota et al., 1986). The DWEL is used as a conservative estimate for the Longer-term HA for an adult. Caution must be exercised when considering the risk of lifetime exposure to dichloromethane because, based on a 2-year inhalation study in rats (NTP, 1986), this chemical is classified as a Probable Human Carcinogen (Group B2). The estimated excess cancer risk associated with lifetime exposure to drinking water containing 1,750 ug/L of dichloromethane is 4×10^{-4} based on the upper 95% confidence limit of the linearized multistage model.

A. PROCEDURES FOR QUANTIFICATION OF TOXICOLOGICAL EFFECTS

1. Noncarcinogenic Effects

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), formerly termed the Acceptable Daily Intake (ADI), is calculated. The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects, even if exposure occurs over a lifetime. The RfD is derived from a No-Observed-Adverse-Effect Level (NOAEL), or Lowest-Observed-Adverse-Effect Level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor. The RfD is calculated as follows:

$$RfD = \frac{(NOAEL \text{ or } LOAEL)}{\text{Uncertainty factor}} = \_\_\_ \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be used in the calculation of the RfD is based on professional judgment while considering the entire data base of toxicological effects for the chemical. To ensure that uncertainty factors are selected and applied in a consistent manner, the Office of Drinking Water (ODW) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980), as follows:

- An uncertainty factor of 10 is generally used when good chronic or subchronic human exposure data identifying a NOAEL are available and are supported by good chronic toxicity data in other species.

- An uncertainty factor of 100 is generally used when good chronic toxicity data identifying a NOAEL are available for one or more animal species (and human data are not available), or when good chronic or subchronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is generally used when limited or incomplete chronic or subchronic toxicity data are available, or when good chronic or subchronic toxicity data identify a LOAEL, but not a NOAEL, for one or more animal species.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than on scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less-than-lifetime study for deriving an RfD, the significance of the adverse health effect, and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium-specific (i.e., drinking water) lifetime exposure, at which adverse, noncarcinogenic health effects are not expected to occur. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{(\text{RfD})(\text{body weight in kg})}{\text{Drinking water volume in L/day}} = \_\_\_\_ \text{ mg/L } (\_\_\_\_ \text{ ug/L})$$

where:

Body weight = assumed to be 70 kg for an adult.

Drinking water volume = assumed to be 2 L per day for an adult.

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (One-day, Ten-day, and Longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated

using a similar equation to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$HA = \frac{(\text{NOAEL or LOAEL})(bw)}{(\_\_\_\ \text{L/day})(UF)} = \_\_\_\_ \text{ mg/L } (\_\_\_\_ \text{ ug/L})$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. One-day HA for a 10-kg child ingesting 1 L water per day.
2. Ten-day HA for a 10-kg child ingesting 1 L water per day.
3. Longer-term HA for a 10-kg child ingesting 1 L water per day.
4. Longer-term HA for a 70-kg adult ingesting 2 L water per day.

The One-day HA calculated for a 10-kg child assumes a single acute exposure to the chemical and is generally derived from a study of less than 7 days' duration. The Ten-day HA assumes a limited exposure period of 1 to 2 weeks and is generally derived from a study of less than 30 days' duration. A Longer-term HA is derived for both a 10-kg child and a 70-kg adult and assumes an exposure period of approximately 7 years (or 10% of an individual's lifetime). A Longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

2. Carcinogenic Effects

The EPA categorizes the carcinogenic potential of a chemical, based on the overall weight of evidence, according to the following scheme:

- Group A: Known Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.

- Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.

- Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.

- Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.

- Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal studies in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable, or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies in animals. To predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less-than-lifetime studies, and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 liters of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit

risk) value together with the assumption for lifetime exposure via ingestion of water. The cancer unit risk is usually derived from a linearized multistage model, with a 95% upper confidence limit providing a low-dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit, and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any others. Because each model is based upon differing assumptions, the estimates that are derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty due to the systematic and random errors in scientific measurement. In most cases, only studies using laboratory animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist such as the incomplete knowledge concerning the health effects of contaminants in drinking water; the impact of the laboratory animal's age, sex, and species; the nature of the target organ system(s) examined; and the actual rate of exposure of the internal targets in laboratory animals or humans. Dose-response data usually are available only for high levels of exposure, not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

B. QUANTIFICATION OF NONCARCINOGENIC EFFECTS FOR DICHLOROMETHANE

Exposure to dichloromethane (DCM) has resulted in hepatic, renal, cardiac, and central nervous system (CNS) toxicity in a variety of species. DCM vapors are irritating to the lungs, mucous membranes, eyes, and skin. The most serious effects of DCM (i.e., severe CNS depression/death) occur following exposure to high vapor concentrations or when large doses are administered via gavage or injection. Such severe effects are unlikely to occur in humans or laboratory animals by exposure to DCM via drinking water.

1. Toxic Effects in Humans

a. Short-term exposure

Toxicity studies on DCM in humans are limited to inhalation exposure. Behavioral and neurological symptoms such as light-headedness (Stewart et al., 1973), reduced scores on sensory/motor tests (Fodor and Winneke, 1971), and eye/hand coordination depression (Putz et al., 1976) have been observed at levels of 800 ppm for 1 hour, 300 ppm for 3 hours, and 200 ppm for 4 hours, respectively. These exposures correspond to approximate doses of 12 to 14 mg/kg (see Appendix for calculation).

Reports of serious health effects from accidental/occupational exposure to DCM (Moskowitz and Shapiro, 1952; Bonventre et al., 1977; Stewart and Hake, 1976) have not adequately determined the circumstances of exposure or quantified airborne DCM concentrations.

After carbon monoxide was found to be a metabolite of DCM, Stewart et al. (1972b) expressed concern that individuals with advanced cardiovascular disease may suffer severe effects from DCM exposure. Elevated carboxyhemoglobin levels

following DCM exposure have been implicated in exacerbation of cardiovascular effects (Welch, 1987), but no conclusive evidence linking DCM to cardiotoxicity in humans has been shown.

b. Long-term exposure

Hepatotoxicity and possible hematopoietic effects have been implicated in chronic occupational exposure studies. Ott et al. (1983c) studied 83 men and 183 women occupationally exposed to DCM levels of 60 to 475 ppm (approximately 7.2 to 57 mg/kg/day; see Appendix). Red blood cell counts were increased in women, but not in men, exposed to approximately 475 ppm DCM, compared with no increase among unexposed controls.

Welch (1987) analyzed 141 cases of adverse health effects in workers occupationally exposed to DCM. Effects included neurotoxicity, respiratory irritation, cardiotoxicity, and hepatitis. Although the author linked these effects to DCM, in none of these cases could it be conclusively demonstrated that the effects were due to DCM exposure. Confounding variables included exposure to other solvents and cigarette smoking. In addition, data on DCM concentrations in workplace air and data on the carboxyhemoglobin levels in the blood of exposed individuals were incomplete.

2. Toxic Effects in Animals

a. Short-term exposure

The only acute oral toxicity study found was that reported by Kimura et al. (1971). In this study, 14-day-old (16 to 50 g), young adult (80 to 160 g), and older adult (300 to 470 g) Sprague-Dawley rats were given single oral doses of DCM (undiluted) and observed for 1 week for mortality and signs of toxicity.

LD_{50} values and 95% confidence limits for 14-day-old, young adult, and older adult rats were 1.8 (1.3 to 2.3), 1.6 (1.3 to 1.9), and 2.3 (1.7 to 3.2) mL/kg, respectively. Although few details were given, the authors report that the lowest dose causing observable effects (i.e., dyspnea, ataxia, cyanosis, and/or coma) was 1 mL/kg (equivalent to 1,326 mg/kg, based on a density of 1.326 g/mL).

Short-term DCM exposure has also been shown to cause a variety of neurotoxic effects in laboratory animals. At concentrations of 17,000 ppm for 6 hours, or 27,000 ppm for 1.5 hours (approximately equivalent to 5,600 and 2,200 mg/kg/day; see Appendix), DCM induced coma and death in rats (Thomas et al., 1971). Rats developed symptoms of depressed activity after 3 hours of exposure to concentrations of 1,000 ppm (approximately 165 mg/kg; see Appendix).

Other neurotoxic effects have resulted from exposure to DCM via inhalation or ip injection. Effects on sleeping behavior such as reduced rapid eye movement (REM) sleep were observed in rats (strain not specified) exposed continuously for 24 hours to concentrations as low as 500 ppm (approximately equivalent to 660 mg/kg; see Appendix; Berger and Fodor, 1968). Other neurological effects include edema of the meninges of the brains of female beagles exposed continuously to 5,000 ppm DCM for 17 to 23 days (MacEwen et al., 1972), and a decrease in sciatic nerve conduction velocity in Wistar rats exposed to 85 and 510 mg/kg via ip injection (Pankow et al., 1979).

Hepatotoxic effects of short-term inhalation exposure to DCM have been demonstrated in several species. Morris et al. (1979) observed increased hepatic triglyceride and phospholipid levels in guinea pigs exposed to 5,200 ppm for 6 hours (approximately 1,400 mg/kg; see Appendix). Male Hartley guinea pigs exposed via inhalation to 11,100 ppm for 6 hours, or 5,000 ppm for 6

hours/day for 5 days, also developed a variety of hepatic histopathological lesions such as fatty livers and vacuolization (Balmer et al., 1976). Hepatic fatty changes were also reported by Balmer et al. (1976) in three of five male Hartley guinea pigs exposed to DCM at levels of 552 to 679 ppm for 6 hours/day for 5 days (approximately 188 mg/kg; see Appendix).

Female mice (ICR strain) exposed continuously via inhalation to 5,000 ppm of technical grade DCM (12,000 mg/kg/day; see Appendix) for 7 days exhibited increased liver-to-body weight ratios, increased liver triglyceride levels, and decreased glycogen and protein synthesis. A variety of histopathological effects including breakdown of the endoplasmic reticulum in hepatocytes, referred to as balloon degeneration, were also observed. Liver lesions were initially noted after 12 hours of exposure or 6,000 mg/kg/day (Weinstein et al., 1972). Male Wistar rats, exposed to 500 ppm for 5 hours/day for 10 days (approximately 140 mg/kg/day; see Appendix), exhibited microsomal enzyme induction (Norpoth et al., 1974).

Klaassen and Plaa (1966) detected minor inflammatory changes to the liver (no details were specified) in male Swiss-Webster mice given a single intraperitoneal (ip) injection of 2,519 mg/kg DCM in corn oil; no histopathological changes were reported for mice administered 1,459 mg/kg. In addition, no changes in SPGT activity were noted at either dose level. Mongrel dogs appeared to be more sensitive to DCM exposure, displaying slight hepatic changes such as subcapsular necrosis, moderate neutrophilic infiltration, and organ dysfunction characterized by increased serum glutamic-pyruvic transaminase (SGPT) activity 24 or 48 hours after receiving a single ip injection of 663 or 995 mg/kg DCM in corn oil. The effective dose at which a 50% increase in organ dysfunction

(ED_{50}) occurred was estimated to be 796 mg/kg, based on increased SGPT activity (Klaassen and Plaa, 1967).

Cornish et al. (1973) also reported elevated serum glutamic-oxaloacetic transaminase (SGOT) levels in groups of four Sprague-Dawley rats administered ip injections of 265, 663, and 1,326 mg/kg DCM in peanut oil.

b. Long-term exposure

Long-term exposure to DCM has been shown to cause a variety of hepatotoxic effects including carcinogenesis, which will be discussed in detail in Section C. In a 90-day study conducted at Bio/dynamics, Inc. (Kirschman et al., 1986), Fischer 344 rats were given DCM in the drinking water at target concentrations of 0.15, 0.45, or 1.50%, which are equivalent to doses of 166, 420, or 1,200 mg/kg/day, respectively, in male rats, and 209, 607, or 1,469 mg/kg/day, respectively, in female rats, based on water consumption measurements. Several hepatocellular changes were observed after 90 days of exposure to DCM (Table 1). A dose-related increase in the incidence of hepatocyte vacuolization (lipid accumulation) was found. Centrilobular necrosis, granulomatous foci, and some evidence of ceroid and lipofuscin accumulation were noted in mid- and high-dose animals, particularly females. Slight decreases in body weight were noted in mid-dose males and high-dose females, and several changes in clinical chemistry parameters, such as increased SGPT, SGOT, and lactic dehydrogenase levels and decreased serum protein levels, were noted, particularly in mid- and high-dose females. The NOAELs for male and female rats were 166 and 209 mg/kg/day, respectively.

Similarly, hepatocellular changes were observed in a companion study in $B6C3F_1$ mice (Kirschman et al., 1986). DCM concentrations of 0.15, 0.45, or

Table 1. Summary of Hepatocellular Findings in the Livers of Rats Given DCM in Drinking Water for 90 Days

Liver response	No. of rats affected at DCM concentrations (%)[a] of:							
	0		0.15		0.45		1.50	
	M	F	M	F	M	F	M	F
Number examined	15	15	15	15	15	15	15	15
Normal	11	4	3	1	6	0	7	0
Hepatocyte vacuolization	1	6	10	13	9	15	7	15
Hepatocyte degeneration	0	0	0	0	0	0	2	12
Pigment, Kupffer cells	0	0	0	0	0	0	1	13
Granuloma (focal)	1	0	0	0	0	4	1	6
Eosinophilic cytoplasmic bodies (hepatocytes)	0	0	0	0	0	0	2	4

[a]These concentrations correspond to doses of approximately 0, 166, 420, or 1,200 mg/kg/day for males and 0, 209, 607, or 1,469 mg/kg/day for females, based on daily water consumption and body weights.

SOURCE: Adapted from Kirschman et al. (1986).

1.50% in drinking water, equivalent to doses of 226, 587, or 1,911 mg/kg/day, respectively, in males, and 231, 586, or 2,030 mg/kg/day, respectively, in females, were administered in mice for 90 days. Livers from the mid- and high-dose males and females exhibited subtle centrilobular fatty changes. In addition, slight decreases in body weights were noted in mid- and high-dose animals during the second half of the study. Unlike rats, male mice appeared to be more sensitive to hepatocellular change compared to females. The NOAELs for this study were 226 and 231 mg/kg/day for male and female mice, respectively.

Bornmann and Loeser (1967) reported that no adverse effects occurred in male and female Wistar rats after administration of 125 mg/L or 15 mg/kg/day (assuming daily consumption of 12 mL/100 g body weight) of DCM in the drinking water for 13 weeks. The urine albumin test was frequently positive, but no biological significance was attached to this observation. Only one dose level was tested, and this was identified as the NOAEL for this study.

Weinstein and Diamond (1972) observed increased triglyceride levels, centrilobular fat accumulation, and decreased glycogen content in livers of female ICR mice exposed continuously to 100 ppm for up to 10 weeks. Histologic effects were first observed after 7 days (approximately 240 mg/kg/day; see Appendix). Haun et al. (1972) observed vacuolization in the livers of rats, dogs, and monkeys (strain not specified) exposed to 100 ppm for 100 days (estimated to be equivalent to doses of 130, 84, and 42 mg/kg/day for rats, dogs, and monkeys, respectively). In this study, rats receiving 25 or 100 ppm exhibited some renal tubular degeneration, but this effect appeared to be transient with subsequent regeneration.

In a chronic study reported by Serota et al. (1986a) and conducted by Hazleton Laboratories, Fischer 344 rats were given DCM in drinking water at target doses of 0, 5, 50, 125, and 250 mg/kg/day for 104 weeks. At 50, 125, or 250 mg/kg/day, an increased incidence of foci/areas of cellular alteration (Table 2) and fatty change were observed in the liver. These hepatic effects were noted at 78 and 104 weeks of the study. An increased incidence of hepatic tumors (neoplastic nodules, and neoplastic nodules and hepatocellular carcinomas combined) occurred in females receiving 50 or 250 mg/kg/day, but not 125 mg/kg/day (see Section C). In addition to hepatocellular effects, statistically significant decreases ($p < 0.05$) in body weight, and in water and food consumption, were observed in animals receiving 125 or 250 mg/kg/day compared with controls. Because the increased incidence of hepatic tumors noted in females was within the range of historical controls, and in the absence of a dose-related effect, i.e., increased incidence in the 125-mg/kg/day group, this was not considered to be attributable to DCM administration. A NOAEL of 5 mg/kg was identified.

Mice appeared to be less sensitive to oral DCM exposure. In a study in which B6C3F_1 mice were given 0, 60, 125, 185, and 250 mg/kg/day DCM in drinking water for 104 weeks, an increase in hepatocellular alterations consisting of slight increases in the amount of Oil Red-O positive material (consistent with increased fat content in the liver) was noted in high-dose males and females. A NOAEL of 185 mg/kg/day was identified (Serota et al., 1986b). Increased incidence of combined heptocellular adenomas/carcinomas was noted in male mice given DCM at concentrations of 125 or 185 mg/kg/day but not at 250 mg/kg/day (see Section C). The authors considered this increase marginal because there was no dose-related response, and the incidence was within the historical

Table 2. Incidence of Liver Foci/Areas of Alteration in Rats Given DCM in Drinking Water for 78 or 104 Weeks

Sex	Incidence[a] of lesion at DCM dose (mg/kg/day) of: 0	5	50	125	250
	78 weeks				
Males	7/20	3/20	15/20	13/20	20/20
Females	3/20	11/20	14/20	16/20	17/20
	104 weeks				
Males	27/36	22/34	35/38	34/35	40/41
Females	17/31	12/29	30/41	34/38	31/34

[a] Number of rats affected/number examined.

SOURCE: Adapted from Serota et al. (1986a).

control range of 5 to 34% (mean 16.1%) for this tumor type in $B6C3F_1$ mice at Hazleton Laboratories (Serota et al., 1986b).

The National Toxicology Program (NTP, 1986) reported that inhalation exposure to 1,000, 2,000, or 4,000 ppm DCM, 6 hours/day, 5 days/week for 102 weeks, resulted in increased incidences of hepatic hemosiderosis, cytomegaly, cytoplasmic vacuolization, necrosis, granulomatous inflammation, and bile duct fibrosis in both male and female F344/N rats. In addition, increased incidences of benign mammary tumors (primarily fibroadenomas) were noted in both male and female rats exposed to 4,000 ppm DCM (see Section C, Table 7). In a companion study (NTP, 1986), 2-year exposure to 2,000 or 4,000 ppm DCM 6 hours/day, 5 days/week, resulted in hepatic cytologic degeneration in $B6C3F_1$ mice. Dose-related increases in the incidence of alveolar/bronchial adenomas and/or carcinomas, and in the number of treated mice bearing multiple pulmonary tumors or hepatocellular adenomas/carcinomas, were also noted (see Section C).

In another chronic inhalation study, 2-year exposure of Sprague-Dawley rats to 500, 1,500, or 3,500 ppm DCM, 6 hours/day, 5 days/week, resulted in hepatic lesions characterized by increased vacuolization in males and females at the 500-ppm level (approximately 165 mg/kg/day; see Appendix). Increases in sarcomas in and around the salivary glands were observed in male rats at the 1,500- or 3,500-ppm exposure levels. Also, female rats exhibited a dose-related increase in total numbers, but not incidence, of benign mammary tumors (see Section C). No effects were noted in Golden Syrian hamsters exposed for 2 years to 500 to 3,500 ppm DCM, 6 hours/day, 5 days/week (Burek et al., 1984).

3. Development of Health Advisories

The limited studies performed to date may not have identified the most sensitive endpoint of DCM toxicity. Available studies on human occupational

inhalation exposure focus primarily on behavioral/neurological effects; possible toxicity to other tissues has not been investigated in detail. Hepatotoxicity from short-term ingestion and inhalation exposure has been observed in mice, guinea pigs, and rats, but behavioral/neurotoxic effects have not been well studied at similar exposure levels. The only report on the acute oral toxicity of DCM is the study of Kimura et al. (1971). Details of the toxic effects and doses tested were not provided.

Long-term ingestion and inhalation studies of DCM in rats have identified the liver as a target organ. In addition, chronic occupational inhalation exposure has been linked to increased bilirubin levels (Ott et al., 1983c), which is suggestive of hepatotoxicity. Oral and inhalation exposures have also been found to cause kidney and CNS effects in laboratory animals.

a. One-day Health Advisory

The study by Kimura et al. (1971) was selected for derivation of the One-day HA for DCM in a 10-kg child because no other adequate acute oral studies of appropriate duration or design were found in the literature. This study identified a LOAEL of 1.0 mL/kg (1,326 mg/kg) in young adult Sprague-Dawley rats on the basis of gross signs of toxicity (i.e., dyspnea, ataxia, cyanosis, and/or coma) following the administration of a single oral dose of DCM. The authors implied that multiple dose levels were administered to define dose response, although details were not reported. The calculations for a One-day HA for a 10-kg child are given below:

$$\text{One-day HA} = \frac{(1{,}326\ \text{mg/kg})\ (10\ \text{kg})}{(1{,}000)\ (1\ \text{L/day})} = 13.3\ \text{mg/L}\ \text{(rounded to 10,000 ug/L)}$$

where:

1,326 mg/kg = LOAEL, based on gross signs of toxicity in rats.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

b. Ten-day Health Advisory

The March 31, 1987, HA for dichloromethane gives a value for the Ten-day HA of 1,500 mg/L, based on the study of Bornmann and Loeser (1967). With the availability of a more recent study, Kirschman et al. (1986), the Ten-day HA value has been revised and is based on the Longer-term HA of 2,000 ug/L for a 10-kg child.

c. Longer-term Health Advisory

Three studies were considered for the calculation of the Longer-term HA (Table 3). In two studies conducted at Bio/dynamics, Inc., and reported by Kirschman et al. (1986), Fischer 344 rats and B6C3F_1 mice were given nominal concentrations of 0.15, 0.45, and 1.50% DCM in the drinking water for 90 days. These levels are equivalent to doses of 166, 420, or 1,200 mg/kg/day, respectively, for male rats, and 209, 607, or 1,469 mg/kg/day, respectively, for female rats; and 226, 587, or 1,911 mg/kg/day, respectively, for male mice, and 231, 586, or 2,030 mg/kg/day, respectively, for female mice. Based on dose-related increases in hepatocyte vacuolization in both males and females and a variety of histopathological changes at the mid- and high-dose levels, a LOAEL of 166 mg/kg/day was identified. In addition, slight decreases were observed in body weights of mid-dose males and high-dose females, and degenerative changes were observed in the hepatocytes of high-dose females. The authors reported a

Table 3. Summary of Subchronic Oral Toxicity Studies Considered for the Development of the Longer-term HA

Reference	Species	Duration	Dose			Effects
			Percent (v/v)	(mg/kg/day) Males	(mg/kg/day) Females	
Kirschman et al. (1986)	Rat	90 days	0.15 0.45 1.50	166 420 1,200	209 607 1,469	LOAEL Dose-related increases in hepatocyte vacuolization; slight decreases in body weight. In females, hepatocellular degeneration and increases in serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, total serum protein, and lactic dehydrogenase.
Kirschman et al. (1986)	Mouse	90 days	0.15 0.45 1.50	226 587 1,911	231 586 2,030	NOAEL Centrilobular fatty change in liver.
Bornmann and Loeser (1967)	Rat	13 weeks	0.013	15	15	NOAEL No effects noted.

NOAEL for mice of approximately 231 mg/kg/day, based on slight centrilobular fatty changes in the livers of mid- and high-dose animals.

Bornmann and Loeser (1967) exposed Wistar rats to DCM in drinking water for 13 weeks and reported a NOAEL of 125 mg/L. This is equivalent to a dose of approximately 15 mg/kg/day, based on daily water consumption of 12 mL/100 g body weight.

The 90-day study reported by Kirschman et al. (1986), in which DCM was administered in drinking water at doses of 166 to 1,469 mg/kg/day to Fischer 344 rats, has been selected as the basis for the Longer-term HA because rats proved to be slightly more sensitive to DCM administration than mice. This study was selected over the Bornmann and Loeser study primarily because a range of doses was used to demonstrate a toxic effect, and a detailed description of the study methods and results was provided.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\frac{(166 \text{ mg/kg/day})(10 \text{ kg})}{(1 \text{ L/day})(1{,}000)} = 1.7 \text{ mg/L (rounded to 2,000 ug/L)}$$

where:

166 mg/kg/day = LOAEL, based on dose-related increased histopathological changes in the livers of rats.

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

d. Reference Dose and Drinking Water Equivalent Level

Caution must be exercised in deciding how to consider possible lifetime exposure to this substance because, based on the available carcinogenicity data, dichloromethane may be classified in Group B2 (Probable Human Carcinogen), according to the EPA guidelines for assessment of carcinogenic risk (U.S. EPA, 1986). Consequently, the assessment of carcinogenic potential must be balanced against the likelihood of occurrence of health effects related to noncarcinogenic endpoints of toxicity.

The two chronic oral toxicity studies reported by Serota et al. (1986a,b) were considered as the basis for calculation of the Reference Dose (RfD) and Drinking Water Equivalent Level (DWEL) (Table 4). Although both studies were adequate, the study with rats is most appropriate for derivation of the DWEL because rats are the more sensitive species. A NOAEL of 5 mg/kg/day was identified in this study. Effects on body weight, hematological parameters, and histopathological changes in the liver (incidence of foci/areas of cellular alteration and/or fatty changes) were observed at higher doses.

The DWEL for a 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(5\ mg/kg/day)}{100} = 0.05\ mg/kg/day$$

where:

5 mg/kg/day = NOAEL based on the absence of liver and blood effects in rats.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Table 4. Summary of Chronic Oral Toxicity Studies Considered for the Development of the Reference Dose and Drinking Water Equivalent Level

Reference	Species (sex)	Route	Duration (weeks)	Dose (mg/kg/day)	Effect
Serota et al. (1986a)	Rat (M/F)	Oral	104	5	NOAEL
				50	Hepatic fatty change, hepatic tumors.
				125	Hepatic fatty change, decreased body weight and food consumption.
				250	Hepatic fatty change, hepatic tumors, decreased body weight and food consumption.
Serota et al. (1986b)	Mouse (M/F)	Oral	104	60	--
				125	--
				185	NOAEL
				250	Hepatic lesions.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.05\ mg/kg/day)(70\ kg)}{2\ L/day} = 1.75\ mg/L\ (rounded\ to\ 2{,}000\ ug/L)$$

where:

0.05 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption by an adult.

C. QUANTIFICATION OF CARCINOGENIC EFFECTS FOR DICHLOROMETHANE

1. Categorization of Carcinogenic Potential

DCM has been shown to be mutagenic in numerous test systems, including Salmonella reversion assays using S. typhimurium strains TA100, TA1535, and TA98 (U.S. EPA, 1985a). The epidemiologic studies (Friedlander et al., 1978; Hearne and Friedlander, 1981; and Ott et al., 1983a,b,c,d,e) have not demonstrated any excessive cancer risk in occupationally exposed workers. However, because of the limitations of these studies (e.g., insufficient followup time), these findings were judged to be inconclusive (U.S. EPA, 1985b).

Three groups have reported results of DCM carcinogenicity bioassays: Serota et al. (1986a,b, conducted by Hazleton Laboratories); the National Toxicology Program (NTP, 1986); and Dow Chemical Company (Burek et al., 1984; Dow, 1982). The results of these bioassays were considered in evaluating the carcinogenic potential of DCM.

Serota et al. (1986a,b) describe studies in which Fischer 344 rats and B6C3F_1 mice were exposed to DCM in drinking water at concentrations equivalent to doses of 0, 5, 50, 125, or 250 mg/kg/day (rats) and 0, 60, 125, 185, or 250

mg/kg/day (mice). A significant increase ($p < 0.05$) in the incidence of neoplastic nodules/hepatocellular carcinomas was observed in female rats exposed to 50 and 250 mg/kg/day compared to matched controls (Table 5). These increases were within the range of historical controls and were considered marginal. Similarly, increases in combined hepatocellular adenomas/carcinomas in male mice were also considered borderline with increases significantly different ($p < 0.05$) from controls in the 125- and 185-mg/kg/day, but not the 250-mg/kg/day, dose groups (Table 6). Based on the incidence of hepatocellular adenomas/carcinomas in male mice, an upper-bound risk estimate for ingestion of DCM in drinking water was calculated (U.S. EPA, 1985b). Using the multistage model, the incremental unit risk estimate for drinking water was estimated to be 3.5×10^{-7} $(ug/L)^{-1}$.

An inhalation study conducted by NTP (1986) serves as the basis for both the qualitative ranking (Group B2, Probable Human Carcinogen) and the quantitative risk assessment. In this study, Fischer 344/N rats and $B6C3F_1$ mice of both sexes were exposed to DCM concentrations of 0, 1,000, 2,000, or 4,000 ppm (rats) and 0, 2,000, or 4,000 ppm (mice) for 6 hours/day, 5 days/week, for 2 years. Significant increases in the benign mammary tumors (primarily fibroadenomas) were observed in high-dose male and female rats from all DCM-dosed groups (Table 7). Significant positive trends for mammary adenoma or fibroadenoma were also noted in male and female groups. The significance of other tumor incidence increases (combined hepatocellular neoplastic nodules/carcinomas, mononuclear cell leukemia, mesotheliomas, adrenal pheochromocytomas and interstitial cell tumors, and combined pituitary gland adenomas/carcinomas) varied with the type of statistical analysis used to evaluate the results. For mice, increased incidences of alveolar/bronchiolar adenonomas and/or carcinomas as well as significant positive trends were found for both sexes (Table 8), and the number of

Table 5. Summary of Findings for Liver Tumors in Rats Given DCM in Drinking Water for 2 Years[a]

Lesion	Dose (mg/kg/day)						
	0	0	5	50	125	250	250[b]
Males							
Neoplastic nodules	4(5)[c]	5(10)	2(2)	3(4)	3(3)	1(1)	4(16)
Hepatocellular carcinomas	2(2)	2(4)	0(0)	0(0)	0(0)	1(1)	0(0)
Combined nodules/ carcinomas	6(7)	7(14)	2(2)	3(4)	3(4)	2(2)	4(16)
Females							
Neoplastic nodules	0(0)	0(0)	1(1)	2(2)	1(1)	4(5)	2(8)
Hepatocellular carcinomas	0(0)	0(0)	0(0)	2(2)	0(0)	2(2)	0(0)
Combined nodules/ carcinomas	0(0)	0(0)	1(1)	4(5)*	1(1)	6(7)*	2(8)*

[a]Lifetime totals.
[b]Recovery group, exposed to DCM for 78 weeks followed by a recovery period of 26 weeks.
[c]Number of animals affected (percent incidence).
*Significantly different from controls ($p < 0.05$) using a combined control incidence of 0/134.

SOURCE: Adapted from Serota et al. (1986a).

Table 6. Summary of Findings for Liver Lesions/Tumors in Male Mice Given DCM in Drinking Water for 2 Years[a]

Lesion	Dose (mg/kg/day)					
	0	0	60	125	185	250
Focal hyperplasia	4(7)[a]	6(9)	14(7)	4(4)	10(10)	13(10)
Hepatocellular adenoma	6(10)	4(6)	20(10)	14(14)	14(14)	15(12)
Hepatocellular carcinoma	5(8)	9(14)	33(17)	18(18)	17(17)	23(18)
Hepatocellular adenoma and/or carcinoma	11(18)	13(20)	51(26)	30(30)*	31(31)*	35(28)

[a]Number of animals affected (percent incidence).
*Significantly different from controls ($p < 0.05$) using a combined incidence of 24/25.

SOURCE: Adapted from Serota et al. (1986b).

Table 7. Summary of Findings for Mammary and Subcutaneous Tumors in Rats Exposed via Inhalation to DCM for 2 Years

Site/tumor	Dose (ppm) 0	1,000	2,000	4,000
Males				
Mammary gland: adenoma or fibroadenoma	0(0)[a]*	0(0)	2(4)	5(10)*
Subcutaneous tissue: fibroma	1(2)	1(2)	2(4)	4(8)
Mammary gland or subcutaneous tissue: adenoma, fibroadenoma, or fibroma	1(2)*	1(2)	4(8)	9(18)*
Females				
Mammary gland: fibroadenoma	5(10)*	11(22)*	13(26)*	22(44)**
Mammary gland: adenoma or fibroadenoma	5(10)*	11(22)*	13(26)*	23(46)**

[a]Number of animals affected (percent incidence).
*Significantly different from controls ($p < 0.05$).
**Significantly different from controls ($p < 0.01$).
Note: A positive trend denoted at control level by an asterisk using incidental tumor tests (actual tests used were not reported).

SOURCE: Adapted from NTP (1986).

Table 8. Summary of Findings for Lung and Liver Tumors in Mice Exposed via Inhalation to DCM for 2 Years

Site/tumor	Dose (ppm) 0	2,000	4,000
Males			
Alveolar/bronchiolar adenoma	3(6)[a]*	19(38)**	24(48)**
Alveolar/bronchiolar carcinoma	2(4)*	10(20)*	28(56)**
Alveolar/bronchiolar adenoma or carcinoma	5(10)*	27(54)**	40(80)**
Hepatocellular adenoma	10(20)	14(29)	14(29)
Hepatocellular carcinoma	13(26)*	15(31)	26(53)*
Hepatocellular adenoma or carcinoma	22(44)*	22(49)	33(67)*
Females			
Alveolar/bronchiolar adenoma	2(4)*	23(48)**	28(58)**
Alveolar/bronchiolar carcinoma	1(2)*	13(27)**	29(60)**
Alveolar/bronchiolar adenoma or carcinoma	3(6)*	30(63)	41(85)
Hepatocellular adenoma	2(4)*	6(13)	22(46)**
Hepatocellular carcinoma	1(2)*	11(23)**	32(67)**
Hepatocellular adenoma or carcinoma	3(6)*	16(33)**	40(83)**

[a]Number of animals affected (percent incidence).
*Significantly different from controls ($p < 0.05$)
**Significantly different from controls ($p < 0.01$).
Note: A positive trend denoted at control level by an asterisk using incidental tumor tests (actual tests used were not reported).

SOURCE: Adapted from NTP (1986).

treated animals bearing multiple pulmonary tumors was also increased over controls. In addition, the incidence of mice with multiple hepatocellular adenomas/carcinomas increased significantly in a dose-related matter. On the basis of these results, NTP concluded that there was some evidence of the carcinogenicity of DCM for male Fischer 344/N rats as shown by an increased incidence of benign neoplasms of the mammary gland; there was sufficient or clear evidence of the carcinogenicity of DCM for female Fischer 344/N rats as shown by an increased incidence of benign neoplasms of the mammary gland; and there was clear evidence of carcinogenicity in male and female $B6C3F_1$ mice as shown by increased incidence of lung and liver tumors. The increased incidence of hepatocellular adenomas/carcinomas was used as the basis for computing the unit risk estimate for inhalation of DCM: 7.5×10^{-8} $(ug/L)^{-1}$ (U.S. EPA, 1985b).

In the study described by Burek et al. (Dow Chemical, 1983), Sprague-Dawley rats and Golden Syrian hamsters (both sexes) were exposed via inhalation to levels of 0, 500, 1,500, or 3,500 ppm DCM, 6 hours/day, 5 days/week, for 2 years. No effects were noted in hamsters. Increases in two tumor types were observed in rats: (1) ventral cervical sarcomas, probably of the salivary gland (male rats only, 1,500- and 3,500-ppm dose groups); and (2) benign mammary tumors (female rats only, increase in total number of tumors, not incidence) (Table 9). In a second study (Dow, 1982), Sprague-Dawley rats were exposed to 0, 50, 200, and 500 ppm DCM. No significant increase in tumor incidence was found.

2. Quantitative Carcinogenic Risk Estimates

The two risk estimates based on hepatocellular adenomas/carcinomas in mice (Serota et al., 1986a,b; NTP, 1986) are similar, with a mean value of 2.1×10^{-7} $(ug/L)^{-1}$ (U.S. EPA, 1985b). The estimated excess cancer risk associated with

Table 9. Summary of Findings for Mammary and Ventral Cervical Tumors in Rats Exposed via Inhalation to DCM for 2 Years

Site/tumor	Dose (ppm) 0	500	1,500	3,500
Males				
Mammary tumor (benign)	7(8)[a]	3(3)	7(7)	14(14)
Total number benign mammary tumors	8	6	11	17
Ventral cervical sarcoma	1(1)	0(0)	5(5)	11(11)*
Females				
Mammary tumor (benign)	79(82)	81(85)	80(83)	83(86)
Total number benign mammary tumors	165	218	245	287
Ventral cervical sarcoma[b]	--	--	--	--

[a]Number of animals affected (percent incidence).
[b]Not reported.
*Significantly different from controls ($p < 0.05$).

SOURCE: Adapted from Burek et al. (1984).

lifetime exposure to drinking water containing DCM at 1,750 ug/L (the DWEL) is approximately 3.7×10^{-4}. This estimate represents the upper 95% confidence limit from extrapolations prepared by the U.S. EPA Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

D. EXISTING GUIDELINES AND STANDARDS

The U.S. EPA (1980a) criterion for DCM in drinking water is 12.4 mg/L based on noncarcinogenic risk. The original U.S. EPA (1980b) Suggested-No-Adverse-Response Levels (SNARLS, presently referred to as Health Advisories) in drinking water were calculated as 13, 1.5, and 0.150 mg/L for One-day, Ten-day, and Longer-term exposures, respectively. The National Academy of Sciences (NAS, 1980) reported One- and Seven-day NAS-SNARLS of 35 and 5 mg/L, respectively, for DCM in drinking water. Recalculation of these data resulted in One- and Seven-day values of 45.5 and 6.5 mg/L, respectively (U.S. EPA, 1987).

The American Conference of Governmental Industrial Hygienists (ACGIH, 1984) recommended a Time-Weighted Average-Threshold Limit Value (TWA-TLV) of 100 ppm (360 mg/m^3) in the absence of exposure to carbon monoxide and a short-term exposure level of 500 ppm. The Occupational Safety and Health Administration (USHA, 1979) established an occupational exposure standard of 1,737 mg/m^3 for 8 hours (TWA) with a 3,474 mg/m^3 ceiling concentration (5 minutes in any 2 hours). The National Institute of Occupational Safety and Health (NIUSH, 1976) recommended an exposure limit of 261 mg/m^3 for 10 hours (TWA).

E. SPECIAL CONSIDERATIONS

High-Risk Populations

Carbon monoxide is a known metabolite of DCM, causing elevated carboxyhemoglobin levels in humans (Ott et al., 1983c,e). The increased concentrations of carboxyhemoglobin may compound cardiovascular effects as suggested by Welch (1987). Thus, although there is no conclusive evidence linking DCM to cardiotoxicity in man, those suffering from advanced cardiovascular disease may constitute a potential high-risk population (Stewart et al., 1972).

F. SUMMARY

The recommended One-day, Ten-day, and Longer-term HA values, the DWEL, and the estimated excess cancer risks are summarized in Table 10.

Table 10. Summary of Quantification of Toxicological Effects for Dichloromethane

	Drinking water concentration (ug/L)	Reference
One-day HA for 10-kg child	10,000	Kimura et al. (1971)
Ten-day HA for 10-kg child	--[a]	Kirschman et al. (1986)
Longer-term HA for 10-kg child	2,000	Kirschman et al. (1986)
Longer-term HA for 70-kg adult	--[b]	Kirschman et al. (1986)
DWEL (100% from drinking water)	2,000	Serota et al. (1986)
Excess cancer risk		
10^{-4}	476	U.S. EPA (1985b)
10^{-5}	48	U.S. EPA (1985b)
10^{-6}	5	U.S. EPA (1985b)

aThe Longer-term HA is used as a conservative estimate of the Ten-day HA.
bThe DWEL value is used as a conservative estimate of the Longer-term HA value for a 70-kg adult.

G. REFERENCES

ACGIH. 1984. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values. 4th Ed. 1980-1984 supplement. pp. 275-276.

Balmer MF, Smith FA, Leach LJ, Yuille CL. 1976. Effects in the liver of methylene chloride inhaled alone and with ethyl alchohol. Am. Ind. Hyg. Assoc. J. 37:345-352.

Berger M, Fodor GG. 1968. CNS disorders under the influence of air mixtures containing dichloromethane. Zentralbl. Bakteriol. 215:517.

Bonventre S, Brennan O, Jason D, Henderson A, Bastos ML. 1977. Two deaths following accidental inhalation of dichloromethane and 1,1,1-trichloroethane. J. Anal. Toxicol. 1:158-160.

Bornmann G, Loeser A. 1967. Zur frage einer chronisch-toxischen wirkung von dichloromethan. Z. Lebensm.-Unters. Forsch. 136:14-18.

Burek JD, Nitschke KD, Bell TJ, Wackerle DL, Childs RC, Beyer JE, Dittenber DA, Rampy LW, McKenna MJ. 1984. Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters. Fund. Appl. Toxicol. 4:30-47.

Cornish HH, Ling BP, Barth ML. 1973. Phenobarbital and organic solvent toxicity. Am. Ind. Hygiene Assoc. J. 34:487-492.

Dow Chemical Company. 1982. Nitschke KD, Bell TJ, Rampy LW, McKenna MJ. Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI. October 11, 1983.

Fodor GG, Winneke H. 1971. Nervous system disturbances in men and animals experimentally exposed to industrial solvent vapors. Proceedings of the 2nd International Clean Air Congress. New York: Academic Press, pp. 238-243.

Friedlander BR, Hearne FT, Hall S. 1978. Epidemiologic investigation of employees chronically exposed to methylene chloride. J. Occup. Med. 20:657-666.

Haun CC, Vernot EH, Darmer KI, Jr., Diamond SS. 1972. Continuous animal exposure to low levels of dichloromethane AMRL-TR-130, paper No. 12. In: Proceedings of the 3rd Annual Conference on Environmental Toxicology, Wright-Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory, pp. 199-208.

Hearn FT, Friedlander BR. 1981. Follow-up of methylene chloride study. J. Occup. Med. 23:660.

Kimura ET, Ebert DM, Dodge PW. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.

Klaassen CD, Plaa GL. 1966. The relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. Toxicol. Appl. Pharmacol. 9:139-141.

Klaassen CD, Plaa GL. 1967. Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. Toxicol. Appl. Pharmcacol. 10:119-131.

Krischman SC, Brown NM, Coots RH, Morgareidge K. 1986. Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice. Food Chem. Toxicol. 24:943-949.

MacEwen JD, Vernot EH, Haun CC. 1972. Continuous animal exposure to dichloromethane AMRL-TR-72-28, SysteMed Corporation report No. W-71005. Wright-Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratories.

Morris JB, Smith FA, Garman RH. 1979. Studies on methylene chloride induced fatty liver. Exp. Mol. Pathol. 30:386-393.

Moskowitz S, Shapiro H. 1952. Fatal exposure to methylene chloride vapor. Arch. Ind. Hyg. Occup. Med. 6:116-123.

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Vol. 3. National Academy Press, Washington, DC.

National Toxicology Program. 1986. NTP technical report on the toxicology and carcinogenesis studies of dichloromethane (methylene chloride) (CAS No. 75-09-2) in F344/N rats and B6C3F$_1$ mice (inhalation studies). Final report. NIH publication No. 86-2562. National Toxicology Program, Research Triangle Park, NC.

NIOSH. 1976. National Institute for Occupational Safety and Health. Criteria for a recommended standard...occupational exposure to methylene chloride. U.S. Department of Health, Education and Welfare (NIOSH). Washington, DC, pp. 1-3, 76-138, 142.

Norpoth K, Witting U, Springorum M, Witting C. 1974. Induction of microsomal enzymes in the rat liver by inhalation of hydrocarbon solvents. Int. Arch. Arbeitsmed. 33(4):315-321.

OSHA. 1979. Occupational Safety and Health Administration. General industry standards. (OSHA) 2206, Revised January, 1978. U.S. Dept. of Labor, Washington, DC.

Ott MG, Skory LK, Holder BB, Bronson JM, Williams PR. 1983a. Health evaluation of employees occupationally exposed to methylene chloride. General study design and environmental considerations. Scand. J. Health 9(Suppl. 1):1-17.

Ott MG, Skory LK, Holder BB, Bronson JM, Williams PR. 1983b. Health evaluation of employees occupationally exposed to methylene chloride. Mortality. Scand. J. Work Environ. Health 9:8-16.

Ott MG, Skory LK, Holder BB, Bronson JM, Williams PR. 1983c. Health evaluation of employees occupationally exposed to methylene chloride. Clinical Laboratory Evaluation. Scand. J. Work Environ. Health 9:17-25.

Ott MG, Skory LK, Holder BB, Bronson JM, Williams PR. 1983d. Health evaluation of employees occupationally exposed to methylene chloride. Twenty-four hour electrocardiographic monitoring. Scand. J. Work Environ. Health 9:26-30.

Ott MG, Skory LK, Holder BB, Bronson JM, Williams PR. 1983e. Health evaluation of employees occupationally exposed to methylene chloride. Metabolism data and oxygen half-saturation pressures. Scand. J. Work Environ. Health 9:31-38.

Pankow D, Gutewort R, Ponsold W, Glatzel W, Tietze K. 1979. Effect of dichloromethane on the sciatic motor conduction velocity of rats. Experientia 35:373-374.

Putz VR, Johnson BL, Setzer JV. 1976. A comparative study of the effect of carbon monoxide and methylene chloride on human performance. J. Environ. Pathol. Toxicol. 2:97-112.

Serota DG, Thakur AK, Ulland BM, Kirschman JC, Brown NM, Coots RH. 1986a. A two-year drinking-water study of dichloromethane in rodents. I. Rats. Food Chem. Toxicol. 24:959-963.

Serota DG, Thakur AK, Ulland BM, Kirschman JC, Brown NM, Coots RH. 1986b. A two-year drinking-water study of dichloromethane in rodents. II. Mice. Food Chem. Toxicol. 24:959-963.

Stewart RD, Fisher TN, Hosko MJ, Peterson JE, Baretta ED, Dodd HC. 1972a. Carboxyhemoglobin elevation after exposure to dichloromethane. Science 176(4032):295-296.

Stewart RD, Fisher TN, Hosko MJ, Peterson JE, Baretta ED, Dodd HC. 1972b. Experimental human exposure to methylene chloride. Arch. Environ. Health 25:342-348.

Stewart RD, Forester HV, Hake CL, Lebrun AJ, Peterson JE. 1973. Human response to controlled exposure of methylene chloride vapor. Report No. NIOSH-MCOW-ENVM-MC-73-7. Milwaukee, WI, Dept. Environmental Medicine, December. p. 82.

Stewart RD, Hake CL. 1976. Paint remover hazard. J. Am. Med. Assoc. 235(4):398-401.

Thomas AA, Pinkerton MK, Warden JA. 1971. Effects of dichloromethane exposure on the spontaneous activity of mice. AMRL-TR72-130, paper No. 13. In: Proceedings of the 3rd Annual Conference on Environmental Toxicology. pp. 223-227.

U.S. EPA. 1980a. U.S. Environmental Progection Agency. Ambient water quality criteria for halomethanes. EPA 440/5-80-051. Office of Water Regulations and Standards. Criteria and Standards Division. Washington, DC.

U.S. EPA. 1980b. U.S. Environmental Protection Agency. Advisory opinion for dichloromethane (methylene chloride). Draft. Office of Drinking Water. Washington, DC.

U.S. Environmental Protection Agency. 1985a. Health assessment document for dichloromethane (methylene chloride). Final report. EPA-700/8-82-004F. Prepared by the Office of Health and Environmental Assessment, Washington, DC.

U.S. Environmental Protection Agency. 1985b. Addendum to the health assessment document for dichloromethane (methylene chloride); updated carcinogen assessment of dichloromethane. Draft. EPA-600/8-82-004FA. Prepared by the Office of Health and Environmental Assessment, Washington, DC.

Weinstein RS, Boyd DD, Back KC. 1972. Effects of continuous inhalation of dichloromethane in the mouse - morphologic and functional observations. Toxicol. Appl. Pharmacol. 23:660-679.

Weinstein RS, Diamond SS. 1972. Hepatotoxicity of dichloromethane (methylene chloride) with continuous inhalation exposure at a low-dose level. AMRL-72-130, paper No. 13. In: Proceedings of the 3rd Annual Conference on Environmental Toxicology, Wright-Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratories, pp. 209-222.

Welch L. 1987. Reports of clinical disease secondary to methylene chloride exposure - a collection of 141 cases. FYI-OTS.0487-0537. George Washington University School of Medicine. Prepared for the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

APPENDIX

Estimations of Dose From Studies of Inhalation Exposure to Dichloromethane

Species	Concentration (ppm)	Duration of exposure (hr/day)	Estimated absorbed dose (mg/kg/day)[a]	Reference
Human: (70 kg; 0.6 m^3/hr)				
Controlled exposures	200	4	12	Putz et al. (1976)
	300	3	14	Fodor and Winneke (1971)
	800	1	12	Stewart et al. (1973b)
Occupational exposures	60	8	7.2	Ott et al. (1983a,c)
	475	8	57	Ott et al. (1983a,c)
Rat: (0.25 kg; 0.0792 m^3/hr)				
	25	24	33	Haun et al. (1972)
	100	24	130	Haun et al. (1972)
	500	5	140	Norpoth et al. (1974)
	500	6	165	Dow (1980)
	500	24	660	Berger and Fodor (1968)
	1,000	3	165	Thomas et al. (1971)
	17,000	6	5,600	Thomas et al. (1971)
	27,000	1.5	2,200	Thomas et al. (1971)
Mouse: (0.025 kg; 0.0144 m^3/hr)				
	5,000	12	6,000	Weinstein et al. (1972)
	100	24	240	Weinstein and Diamond (1972)
Guinea pig: (0.50 kg; 0.133 m^3/hr)				
	5,200	6	14,400	Morris et al. (1979)
Dog: (10 kg; 0.20 m^3/hr)				
	100	24	84	Haun et al. (1972)
Monkey: (10 kg; 0.1 m^3/hr)				
	100	24	42	Haun et al. (1972)
Hamster: (0.10 kg; 0.0366 m^3/hr)				
	500	6	1,900	Dow (1980)

[a] Estimated absorbed dose was calculated as follows:

$$\text{Dose} = \frac{[\text{Conc.(ppm)} \times 3.47\ \text{mg/m}^3\ \text{ppm}^{-1}][\text{Exposure(hr)}][\text{Resp. rate(mg/m}^3)][50\%\ \text{absorption}]}{\text{body weight (kg)}}$$